The influence of Melatonin on nocturnal hypertension in adolescents with T1DM

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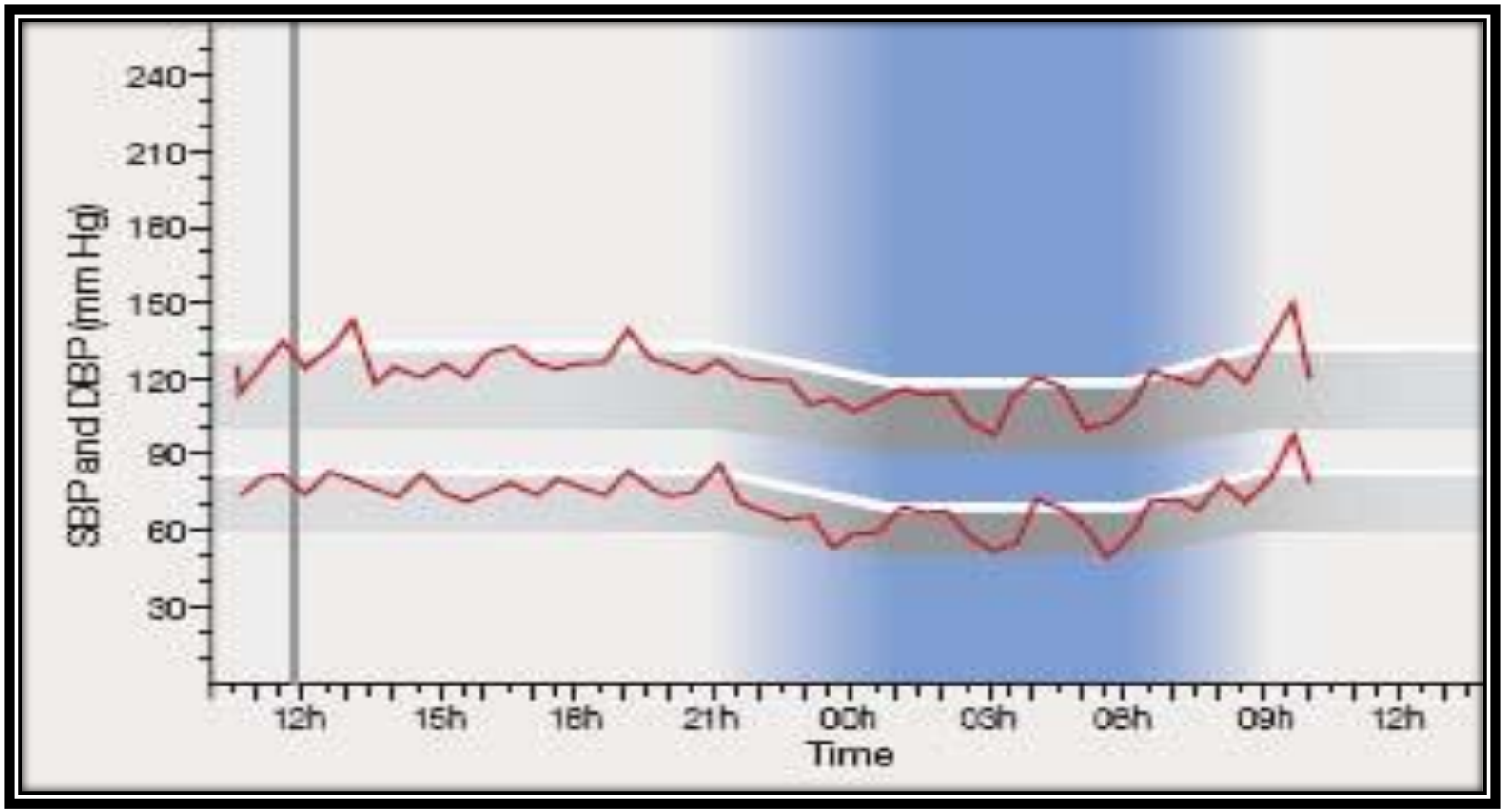
Scientific Background

- Type 1 diabetes is associated with arterial hypertension.
- Atherosclerosis and cardio-vascular disease (CVD) are the major causes of morbidity and mortality in these patients.
- One of the earliest signs of CVD is loss of the physiologic nocturnal blood pressure dip.

Nocturnal dip

- blood pressure drop at night compared to daytime values



The pediatric population

- Incidence of T1DM varies from 8 to 17 per 100,000 in Europe and the U.S.
- The risk for CVD in diabetic patients emerges during childhood.
- Up to 16% of adolescents with T1DM suffer from hypertension.
- Many normotensive patients may have a loss of the physiologic nocturnal drop in BP and this correlates with early vascular changes.
- These early changes frequently lead to frank hypertension later on.

Cavallo A et al. *J of pineal research* 2004

ABPM

- Ambulatory blood pressure monitoring (ABPM) is a useful non-invasive method to detect nocturnal hypertension.
- Useful to determine whether a patient is a dipper or non-dipper.
- It reduces the white coat hypertension effect.
- It can be programmed to record blood pressure in chosen intervals (we use 30 minute intervals).

Melatonin

- Melatonin is a hormone secreted from the pineal gland at night.
- It plays a cardinal role in sleep regulation.
- During adolescence, total sleep duration changes. The circadian timing system responsible for this phase delay in sleep is influenced by hormonal changes specifically a delay in melatonin secretion.

Melatonin and Hypertension

- Recent studies suggest that melatonin may influence the cardiovascular system in humans.
- Vascular melatoninergic receptors/sites have been demonstrated and are functionally linked with vasoconstrictor or vasodilatory effects.
- Studies in hypertensive adults treated with melatonin compared to placebo have shown a reduction in nocturnal hypertension.

Study design

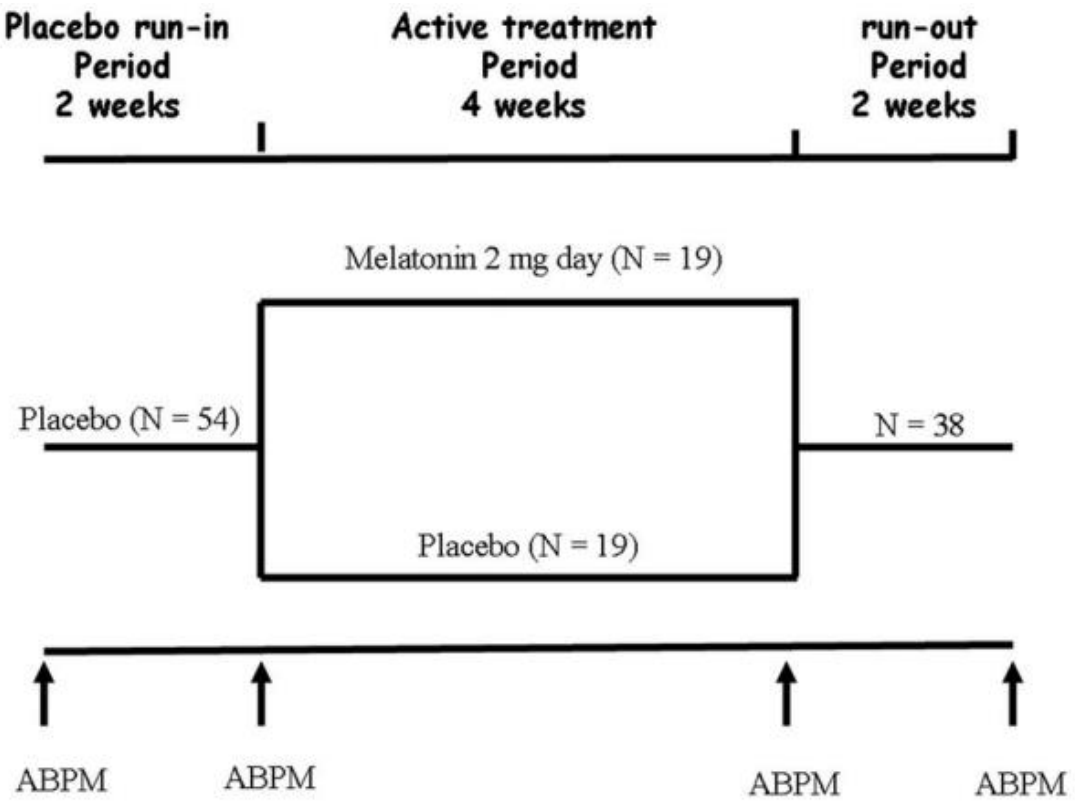
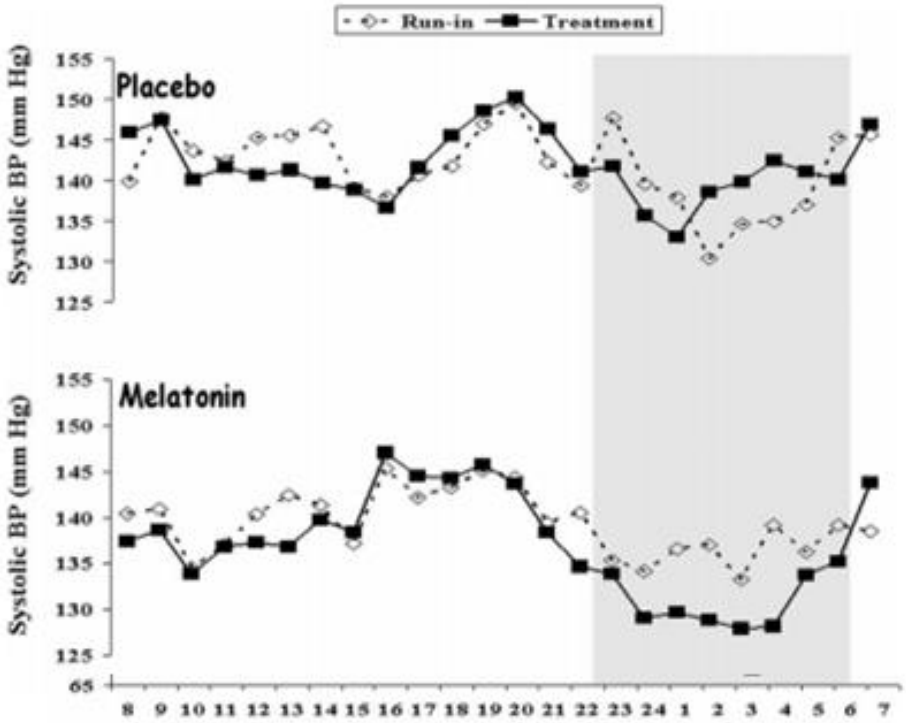
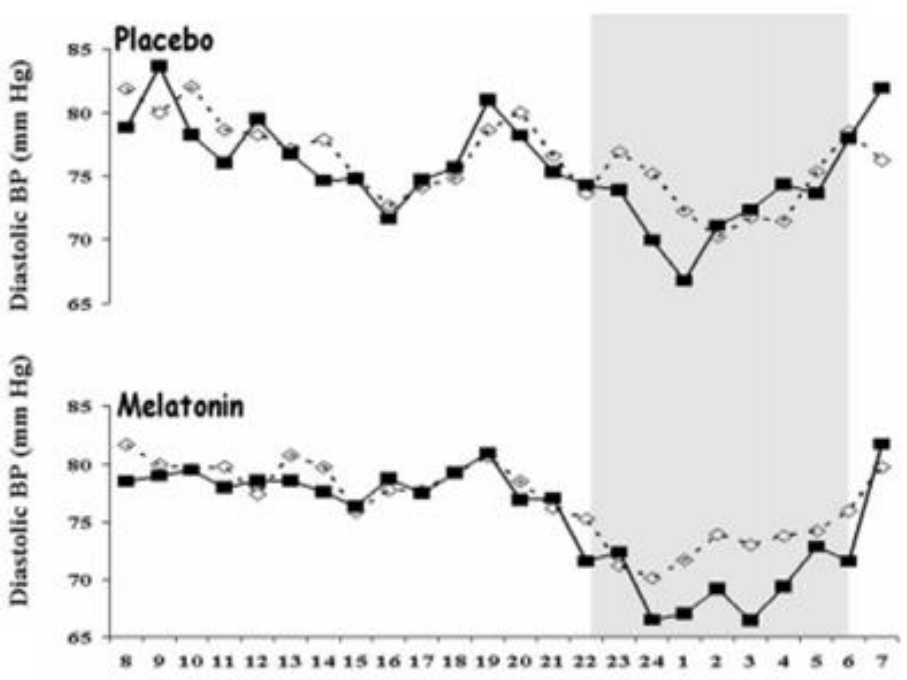


Figure 1 Study design. Patients were screened according to blood pressure levels recorded with ambulatory blood pressure monitoring (ABPM). After screening, patients received placebo for 2 weeks and had another ABPM to confirm the diagnosis of nocturnal hypertension. Patients were then randomized to receive either placebo or melatonin for 4 weeks, and then all patients continued with placebo (run-out period) for 2 weeks. **Arrows** indicate time of ABPM.

Grossman et al. *The Am J of Med* 2006

Melatonin reduces nocturnal blood pressure





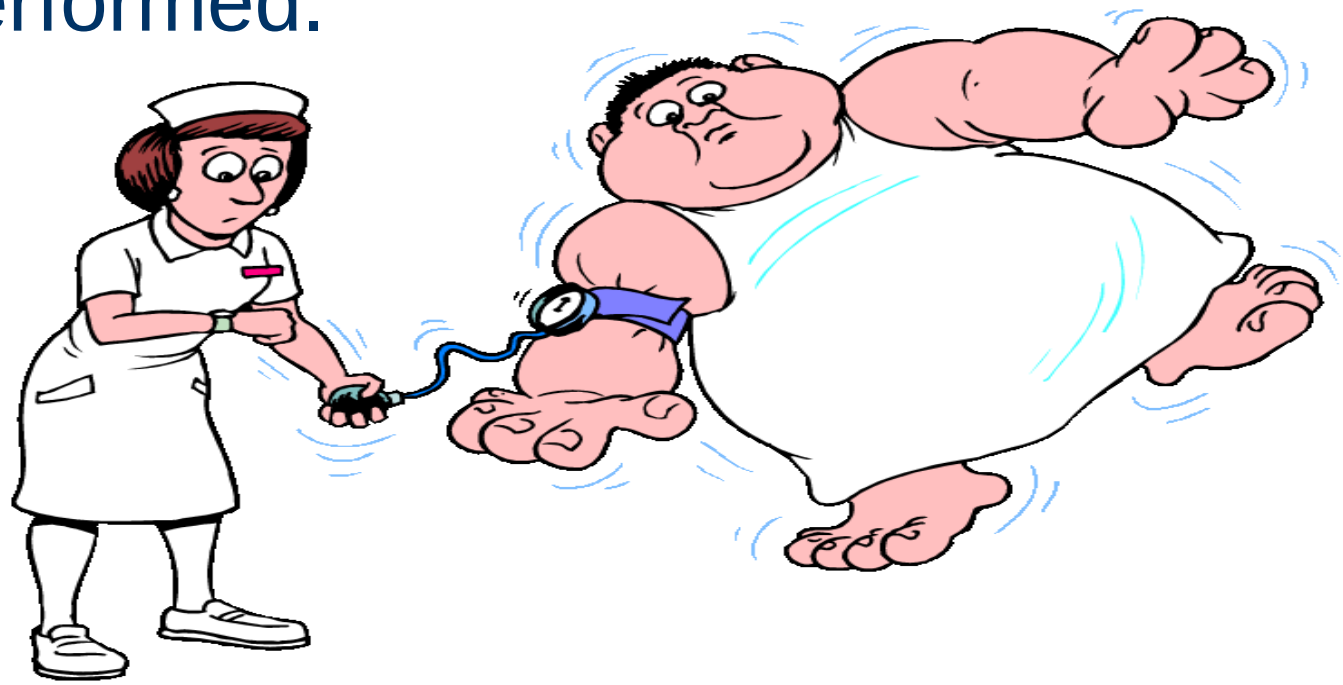
Grossman et al. *The Am J of Med* 2006

Aim of the study

Hypothesis: Treatment with melatonin may improve both nocturnal blood pressure and endothelial function, which would be a desired outcome in diabetic adolescents already at risk of microvascular complications.

Study design

Phase 1: Cross sectional analysis: Each subject will have a 24 hour ABPM performed.



Group study

Inclusion Criteria :

- adolescents ages ranging from 12-19
- At list 3 years since diagnosis with T1DM.

Exclusion criteria:

- Patients receiving BP lowering drugs.

Results - Cohort characteristics

N= 64
Sex distribution: 59% males, 41% females.
Age=15.4y (±2.54)
Mean A1C = 8.2 mg% (±1.71)
BMI=21.8 (±3.87)
Diabetes duration= 7.1y (±3.65)
Systolic blood pressure= 110.43 mmHg (±18.21)
Diastolic blood pressure= 66.9 mmHg (±8.26)
HR= 83.1 BPM (± 12.85)
Weight= 58.44 Kg (±15.8)
Height= 163 cm (±10.6)

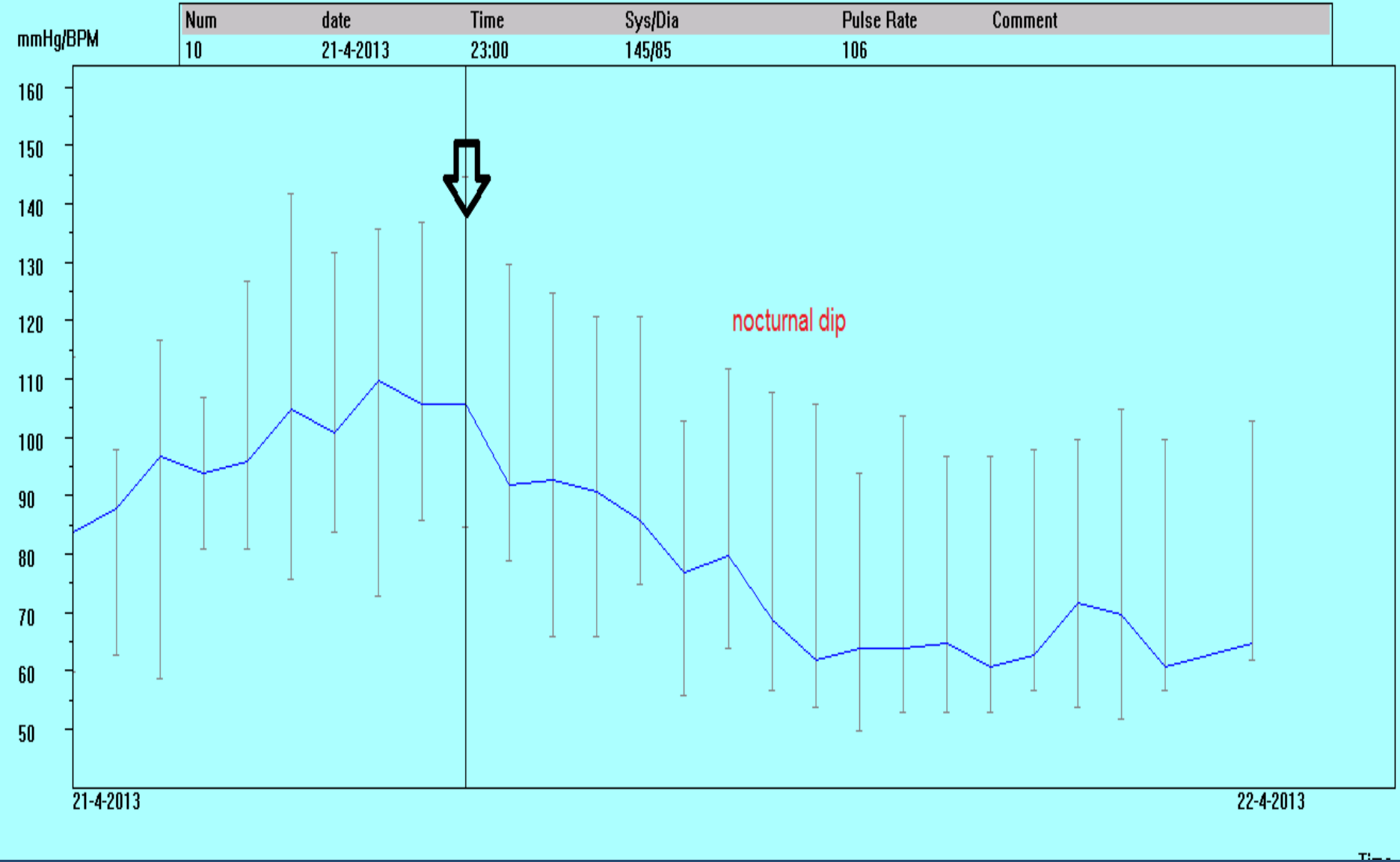
95 %ile of BP in children

	BOYS		GIRLS	
	Systolic	Diastolic	Systolic	Diastolic
3	100	59	100	61
4	102	62	101	64
5	104	65	103	66
6	105	68	104	68
7	106	70	106	69
8	107	71	108	71
9	109	72	110	72
10	111	73	112	73
11	113	74	114	74
12	115	74	116	75
13	117	75	117	76
14	120	75	119	77
15	120	76	120	78
16	120	78	120	78
17	120	80	120	78
18	120	80	120	80

Study protocol

- Patients are recruited to the study during a clinic visit.
- Patients and parents receive an explanation about the study and give their consent to participate.
- Patients who are recruited, are connected to ABPM at home by the research assistant.

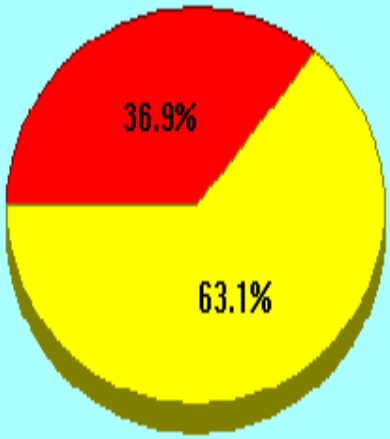
RESULTS


mmHg/BPM
Num
date
Time
Sys/Dia
Pulse Rate
Comment
10
21-4-2013
23:00
145/85
106
160
150
140
130
120
110
100
90
80
70
60
50
nocturnal dip
21-4-2013
22-4-2013

Maximum: 145 (mmHg) (23:00)

Minimum: 94 (mmHg) (03:30)

Averages: 114 (mmHg)



Systolic (mmHg)

120 Above

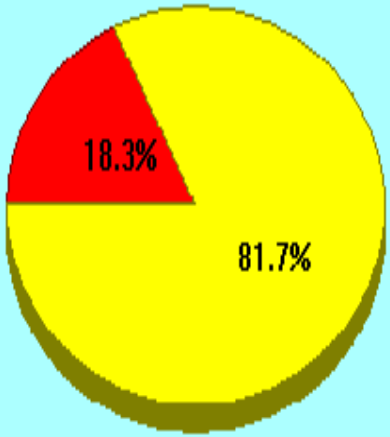
120-120 mmHg

120 Below

Maximum: 86 (mmHg) (22:30)

Minimum: 50 (mmHg) (03:30)

Averages: 65 (mmHg)



Diastolic (mmHg)

80 Above

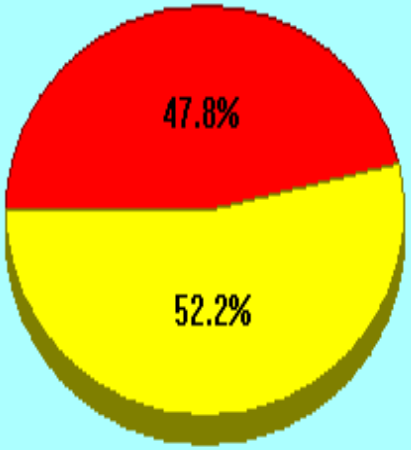
80-80 mmHg

00 Below

Maximum: 145 (mmHg) (22:00)

Minimum: 99 (mmHg) (05:30)

Averages: 121 (mmHg)



Systolic (mmHg)

120 Above

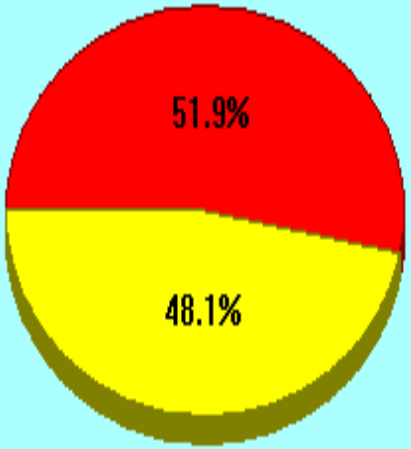
120-120 mmHg

120 Below

Maximum: 93 (mmHg) (22:00)

Minimum: 61 (mmHg) (03:30)

Averages: 78 (mmHg)



Diastolic (mmHg)

80 Above

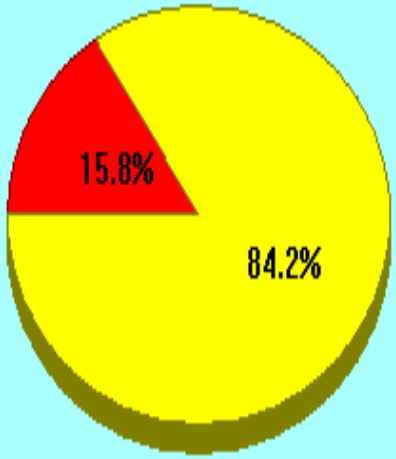
80-80 mmHg

80 Below

Maximum: 131 (mmHg) (21:31)

Minimum: 83 (mmHg) (02:30)

Averages: 99 (mmHg)



Systolic (mmHg)

113 Above

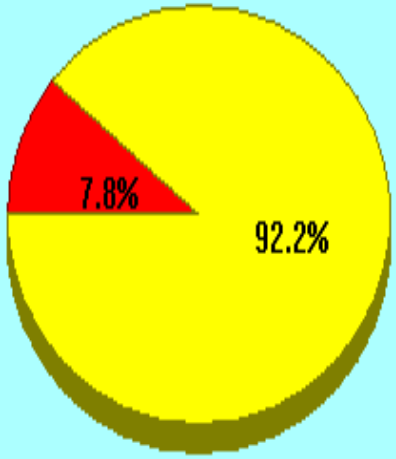
113-113 mmHg

113 Below

Maximum: 110 (mmHg) (21:31)

Minimum: 31 (mmHg) (02:30)

Averages: 54 (mmHg)



Diastolic (mmHg)

74 Above

74-74 mmHg

74 Below

Next Phase

- Phase 2: Adolescents who were detected as non-dippers during phase 1 will be recruited to an interventional trial comparing treatment with melatonin vs. placebo, and repeat ABPM.